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14. ABSTRACT Lymphedema is a common complication of primary breast cancer therapy. It is a chronic, insidiously progressive, and potentially devastating condition. Radiation increases patients' lymphedema risk as conventional fields encompass functioning lymphatics. Imaging technologies may identify these lymphatics and allow tailoring of radiation fields to minimize radiation exposure while preserving regional tumor control. This study uses SPECT scanning to localize lymphatics critical for arm drainage after surgical removal of axillary lymph nodes. The study has established the feasibility of fusing SPECT images with high resolution CT scans used in radiation simulation. Furthermore the study has demonstrate that fusing allows precise quantification of radiation dosimetry delivered to lymph nodes critical for arm drainage. The study will test the hypothesis that increased arm volume correlates with high levels of radiation dosimetry. The fact that higher doses of radiation and larger radiation ports are associated with an increased incidence of lymphedema (volume $\uparrow \geq$ 150ml.), particularly severe lymphedema (volume $\uparrow \geq$ 400ml.), supports this hypothesis. The proposed study realizes the BCRP goals by elucidating a novel means of refining breast cancer treatment to minimize patients' risk of developing the most prevalent and dreaded complication of conventional therapy, lymphedema.

15. SUBJECT TERMS
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Introduction:

This career development award has dual aims. As a training award, the first aim involves the recipients' completion of a Masters degree in Clinical Epidemiology with an emphasis on research methodology and biostatistics. The second aim involves completion of a prospective cohort study to determine whether radiation dosimetry delivered to lymphatics essential for arm drainage correlates with increased arm volume. Lymphedema is the number one survivorship issue in breast cancer (American Cancer Society). Affected patients experience diminished quality of life and are more likely to develop social, vocational, psychological and functional decline (Maunsell, Passik). Current imaging approaches, e.g. SPECT scanning, may permit the precise localization of lymphatics critical for arm draining after axillary surgery (Czerniecki, Joensuu, Witte). Fusion of SPECT images with CT scans used in radiation simulation offers the potential to precisely quantify radiation dosimetry to lymphatics (Chao). Quantification allows biostatistical testing of the hypothesis that increased radiation exposure will correlate with increased arm volume (Liljegren, Meek). Testing of this hypothesis and establishing the feasibility of SPECT-CT fusions are requisite initial steps in the development of radiation planning techniques that exclude lymphatics critical for arm drainage, thereby reducing lymphedema risk.

Body:

Prior to each section of the report, relevant text from the initial Statement of Work has been included.

Task 1. Complete course work and thesis preparation for a Masters of Science degree in clinical epidemiology and the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

a. Course work - Classes will be taken over the course of four semesters at the CCEB (Months 1 - 24)
b. Thesis completion - The thesis will be written under the guidance of a senior CCEB faculty member. This will be completed during the third year of study. (Months 25 - 36)

Dr. Cheville, was awarded the degree of Master of Clinical Epidemiology on May 15, 2006. All requisite coursework (refer to Appendix A, annual report submitted May 29, 2006) and preparation of her Masters thesis (Appendix B, annual report submitted May 29, 2006) was completed in accordance with the timeline initially proposed in the Statement of Work. The recipient's intended the research project proposed in the initial career development award to serve as the focus of her Masters thesis. Due to slow subject recruitment, sufficient data would not have been collected within the three year interval proposed for completion of her Masters Degree. For this reason, an alternate thesis project was proposed to the faculty of the Center for Clinical Epidemiology and Biostatistics and accepted.

Dr. Cheville analyzed a large cross-sectional dataset collected from Stage IV breast cancer patients for the purpose of characterizing rehabilitation needs and service utilization. Important findings included: 1. Physical impairments were identified in 150 (92%) subjects, and 144 subjects (88%) required some type of rehabilitative intervention; 2. Physical impairments that required hospitalization were overwhelmingly more likely to receive rehabilitation, OR 87.88 (95% CI 28.46 - 271.36), and PT/OT, OR 558.75 (95% CI 186.99 - 1669.61); 3. Minorities and patients of lower socioeconomic were significantly less likely to receive rehabilitation services. These findings have not been previously reported in the cancer literature. The manuscript is currently undergoing revision and text reduction in preparation for submission to the Journal of the National Cancer Institute.

Task 2. Conduct a prospective cohort study to estimate the risk of lymphedema associated with radiation dosimetry to lymph node critical for arm drainage. (Months 1-36)

a. Subject enrollment - A total of 50 subjects will be enrolled in the study. An average of 130 TXN1M0 breast cancer patients is seen at the University of Pennsylvania Cancer Center each year. Estimating a conservative accrual rate of 3 patients per month, subject enrollment will require 17 months. (Months 1-17).

Contingent on the approval of the USAMRMC HSRRB, subject enrollment may commence prior to the dispensation of the BCRP Physician Scientist Training Award.

b. Data Collection - Once enrolled, subjects will be followed for 12 months. Data will be collected at 2 time points: **A**. baseline (prior to radiation therapy), **B**. 12 months after initiation of radiation therapy. (Months 1 - 29)
c. Institutional Review Board approval - This protocol has been approved by the University of Pennsylvania Institutional Review Board and the University of Pennsylvania Cancer Center Clinical Trials Scientific Review and Monitoring Committee. The protocol has been submitted to the USAMRMC HSRRB and approval is pending. (Completed prior to Physician Scientist Training Award dispensation)
d. Data entry - Data entry will occur concurrently with data collection. All data will be entered one month following the completion of data collection. (Months 1 - 30)
e. Data analysis - Data analysis will commence following completion of data entry. It is anticipated that analysis will require two months. (Months 31 - 32)
f. Manuscript preparation - Preparation of manuscripts will require 4 months. (Months 32 - 36).

a. Subject enrollment

Thirty seven subjects have enrolled in the study as of October 2nd, 2006. Subject recruitment was delayed by the need for the approval of three regulatory bodies; the USAMRMC Review Board, the University of Pennsylvania Institutional Review Board, and the Abramson Family Cancer Institute Clinical Trials Committee. Recruitment was further delayed by the need to determine the optimal: amount of radiolabeled tracer for subdermal injection, upper extremity injection sites, and interval between tracer injection and SPECT scanning. Recruitment has been slower than planned for in the statement of work. Nonetheless, 2-3 patients have been enrolled each month.

b. Data collection

Complete 12-month data has been collected on 12 subjects, six-month data on 17 subjects, and initial data on 37 subjects. Analysis of the initial data has revealed less variance in arm volume than was used in the initial power analysis. With 37 subjects and a two-sided α of .05, we can detect a 4.7% change in inter-limb volume discrepancy with 80% power, a 5.5% discrepancy with 90% power, and a 7.4% discrepancy with 99% power. Each of these limb volume discrepancies is far smaller than the 15% difference which is generally considered clinically significant. Therefore, we are adequately powered with 37 subjects to address the specific aims outlined in the initial proposal. Given the cost to subjects of time and energy, in the face of little associated personal benefit, no additional subject recruitment is necessary or ethically defensible.

c. Institutional Review Board approval

Approvals for the study have been obtained and appropriately renewed from the USAMRMC Review Board, the University of Pennsylvania Institutional Review Board, and the Abramson Family Cancer Institute Clinical Trials Committee.

d. Data Entry

A Microsoft Access database has been constructed which includes subjects' sociodemographic and cancer treatment-related variables. The database contains missing values which will require further chart extraction to remedy. The physicist in the Radiation Oncology Department has established that a new computer program must be generated to precisely quantify lymph node radioactive tracer uptake.. The program will three dimensionally assess tracer count activity on SPECT images. A programmer will be hired to perform this task. It is anticipated that the task will require 6 months at 50% effort. This work will be completed at the Mayo Clinic, Rochester Minnesota.

e. Data Analysis

Descriptive statistics of cancer treatment-related, SPECT scan and dosimetry results have been calculated for preparation of platform and poster presentations. Fifty percent (18) of the enrolled subjects had sentinel lymph node dissections alone, while the other 50% underwent $\geq$ 2-level surgical axillary clearing. Sixteen subjects (53%) had right-sided breast cancer. Thirteen subjects (43%) underwent modified radical mastectomies, while seventeen (57%) elected for breast conservation therapy. Thirteen patients (43%), a slightly different subgroup, received radiation to breast tangents while the remaining subjects received four field) irradiation tangents, posterior axillary boost, and supraclavicular fields).

The lymph node (LN) distribution was 1-10 with a mean of 3 LNs/patient distributed through out axillary and supraclavicular LN beds. No lymph nodes were visualized in 3 patients (8.1%). We suspect this may reflect a technical error rather than true absence of LNs. None of the three patients experienced arm, breast, or axillary swelling. Level I nodes were visualized in the lateral axilla in 62.5% of cases and in the medial axilla in 68.8% of cases. Level II/III nodes were detected in 50% of patients. Supraclavicular lymph nodes were visualized in 56.3% of cases.

Dosimetry measurements in the 22 subjects that have been carefully analyzed indicates that the LNs draining the arm frequently receive the full prescribed radiation isodose (46 – 50 Gy) irrespective of location. Sixty seven LNs were identified among 22 subjects, for a mean of 3.05 LN per subject. The mean radiation dose per LN was 28.47 (SD 22.01). The distribution of LN dosimetry is graphically illustrated (Figure 1) by

radiation treatment groups. LNs in subjects undergoing 4-field (35.72 Gray) versus breast tangent (19.54 Gray) radiation, on average, received significantly greater dosimetry (p=0.0001, ttest). However, in 63.3% of subjects treated with breast tangents, at least 1 LN received ≥44 Gray. Figure 2 illustrates the distribution of maximal LN dosimetry by treatment group.

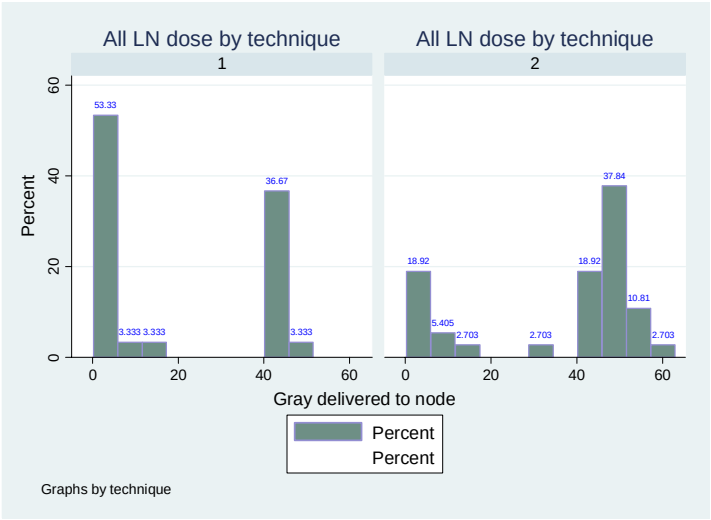

Figure 1.

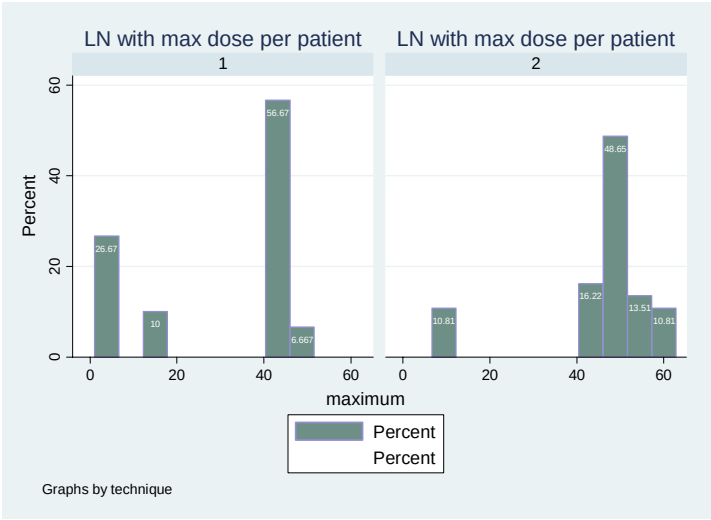

Figure 2.

Subjects who had undergone two-level axillary dissections were more likely to have >4 LNs identified on CT-SPECT (p = 0.006, X^2). This finding is physiologically relevant. It has been long appreciated that roughly 40% of breast cancer patients who undergo aggressive treatment, e.g. modified radical mastectomy, full surgical axillary LN clearing, and four-field irradiation, do not develop lymphedema. The mechanism by which the lymphatic system compensates for extensive lymph node loss has remained obscure. Our results suggest that collateral drainage pathways involving multiple LNs develop after surgical removal of the LNs congenitally 'assigned' to drain the arm. This finding is clinically relevant since it supports the need to develop clinical strategies to enhance lymphatic collateralization during and immediately following primary breast cancer treatment.

f. Manuscript Preparation

The results of this study are relevant to audiences from different medical disciplines including nuclear medicine, radiation physics and oncology, and lymphology. For this reason three manuscripts with separate emphases are being prepared. The first will describe the lymph node mapping and SPECT scanning techniques. This paper will be submitted to a nuclear medicine journal. The second will report the SPECT and simulation CT image fusion strategy used for quantification of radiation dosimetry. The third will describe how our findings support current unsubstantiated beliefs regarding the collateraization of lymph pathways following surgical resection of axillary nodes.

Key Research Accomplishments

1. Development of mapping strategy to identify LN essential for arm drainage after surgical axillary LN removal for primary breast cancer.

2. Precise anatomic localization of LNs draining the arm using eINTEGRA SPECT scanning.

3. Fusion of eINTEGRA scans with CT simulation images used in radiation planning with the potential to develop individually tailored radiation fields based on the location of physiologically relevant LNs.

4. Accurate quantification of radiation dosimetry delivered to LN essential for arm drainage following surgical manipulation of the axillary LN bed (e.g. sentinel LN biopsy or 2-level axillary clearing).

5. Construction of individually tailored fields that minimize radiation exposure to the LNs draining the arm using conventional intensity modulated radiation therapy techniques.

6. Discovery of the evidence supporting lymphatic collateralization following removal of LNs congenitally predisposed to drain the arm.

Reportable Outcomes

1. Presentation of Grand Rounds to the Department of Physical Medicine and Rehabilitation at the Mayo Clinic, Rochester Minnesota. November, 2005.

2. Presentation of Grand Rounds to the Department of Physical Medicine and Rehabilitation at the Medical College of Wisconsin. June, 2006

3. Platform presentation at the American Society of Nuclear Medicine. June, 2006

4. Poster presentation accepted to the European Society of Therapeutic Radiation Oncology meeting in October, 2006.

5. Platform presentation accepted for the National Lymphedema Network meeting in November, 2006.

Conclusion

Work to date has established that LNs draining the arm after surgical manipulation of the axilla in the context of primary breast cancer can be localized using eINTGRA SPECT scanning. The radiation dose delivered to LNs can be quantified by fusing eINTEGRA SPECT images with radiation simulation CT scan images. This work creates the possibility of constructing radiation fields that minimize dosimetry to LNs draining the arm. Customized radiation fields may be considered for patients with 'low risk' breast cancers (e.g. small tumor, hormone receptor positive, benign histopathological characteristics, and negative sentinel LNs). At this point the association between reduced LN dosimetry and reduced lymphedema risk remains theoretical. Complete data collection will allow empiric evaluation of the proposed association. The fact that more LNs were visualized in patients who underwent $\geq$2-level axillary clearing suggests that lymph collateralization is an important means of re-establishing lymphatic homeostasis. This finding justifies the development of techniques to enhance this endogenous compensatory mechanism.

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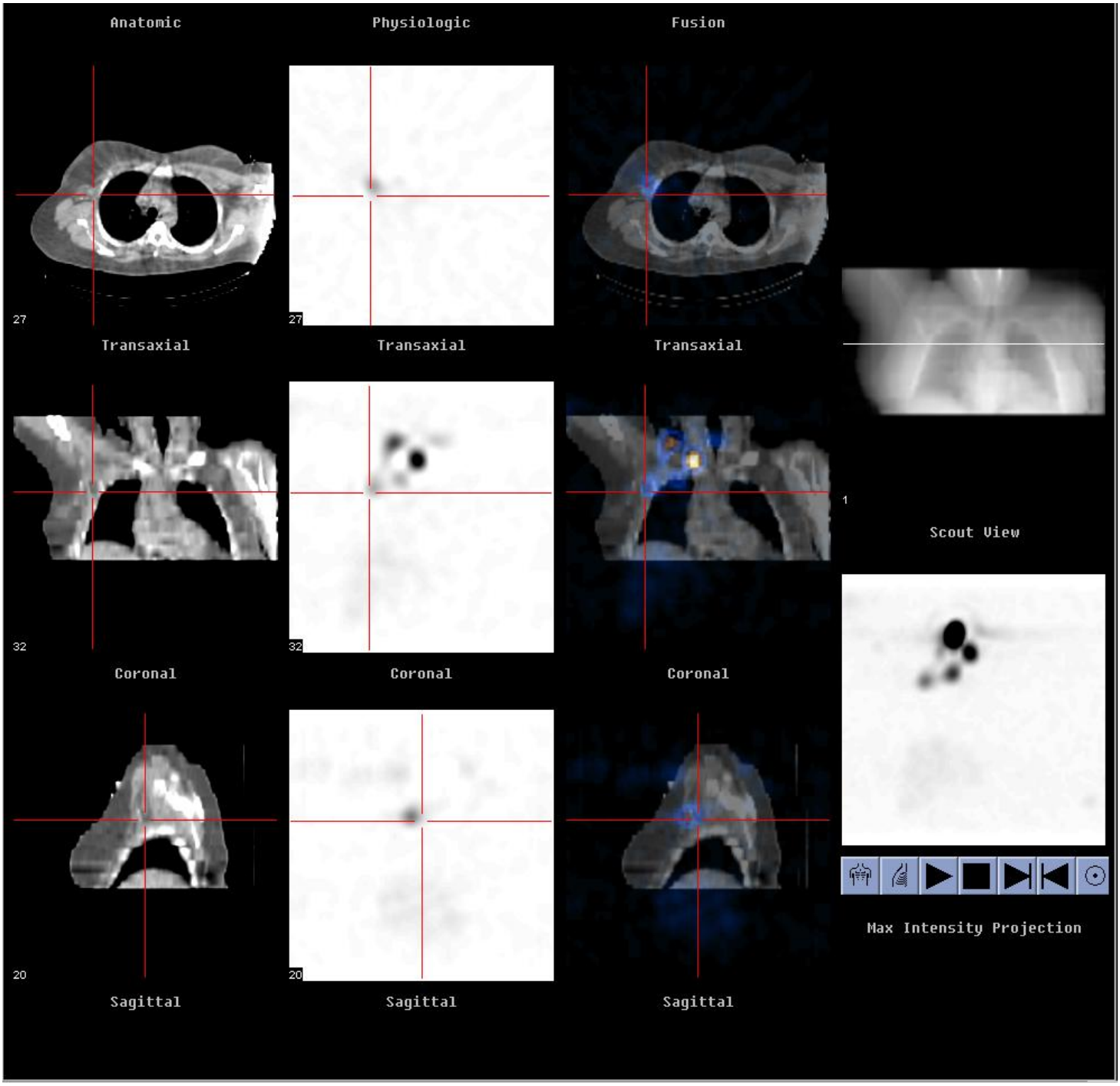
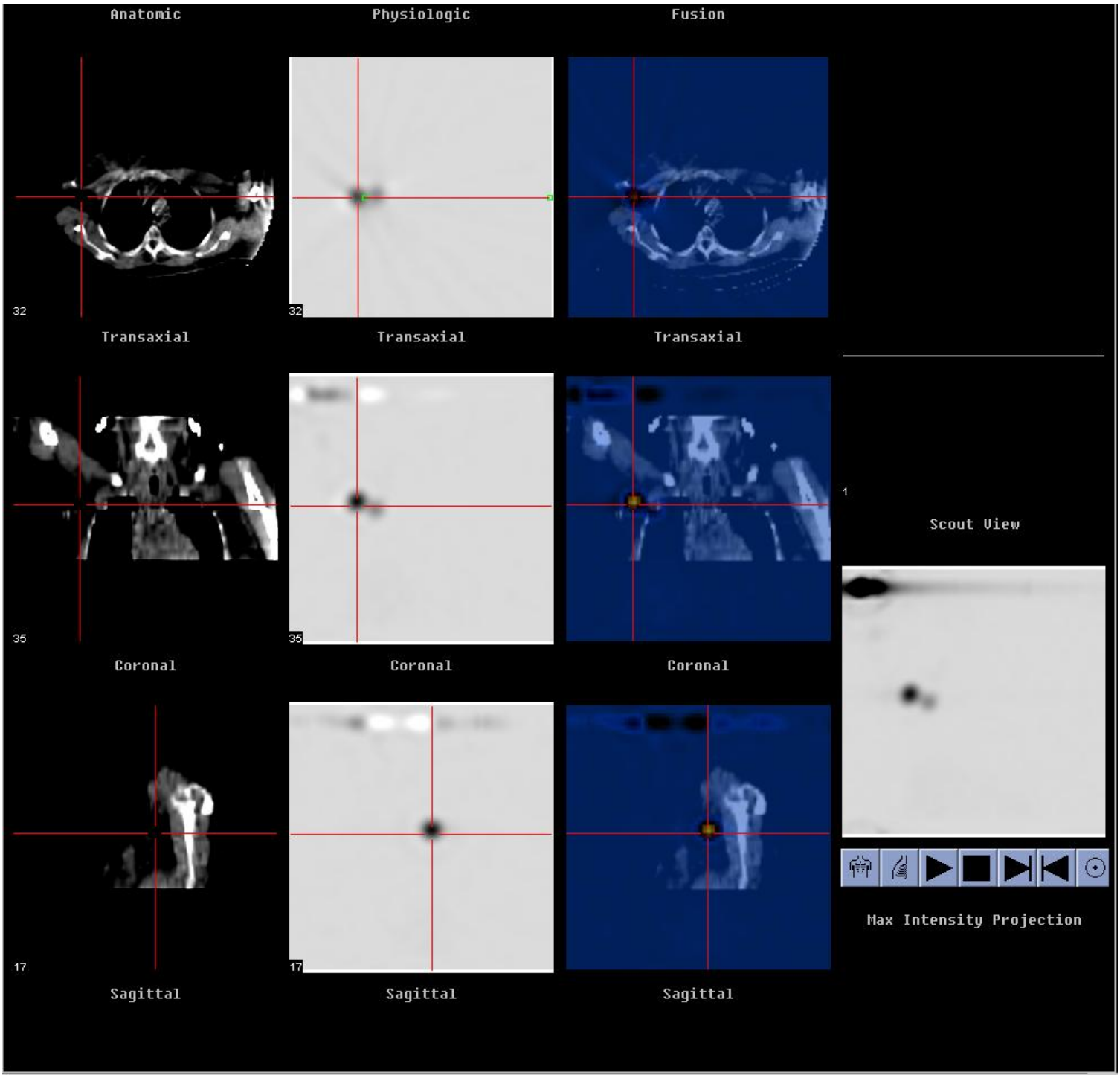
Supporting Data

eINTEGRA SPECT scans from 2 study subjects




Anatomic
Physiologic
Fusion
32
32
Transaxial
Transaxial
Transaxial
35
35
Coronal
Coronal
Coronal
17
17
Sagittal
Sagittal
Sagittal
1
Scout View
Max Intensity Projection